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**IND 50,269**

July 16, 1999

Paul Leber, M.D.
Division Director
Food and Drug Administration
Division of Neuropharmacological Drug Products (HFD-120)
Woodmont 2
1451 Rockville Pike
Rockville, MD 20852

**SUMMARY:** Annual Report of Progress – IND# 50,269 (mifepristone)

Investigational Study Titles: "Rapid reversal of psychotic depression using mifepristone"
"Treatment of schizoaffective disorder using mifepristone"

Number of Patients Treated to Date: 8

Most Recent Subject Enrollment Date: July 12, 1999

Adverse Reactions Encountered: none.

Modifications to the Protocol(s): none.

Dear Dr. Leber:

We continue to use mifepristone in our protocols "Rapid reversal of psychotic major depression using mifepristone (RU 486)" and "Treatment of schizoaffective disorder using mifepristone." To date, we have been impressed by its relative lack of side effects and its potential efficacy. We have received no subjective complaints from any of the research subjects while they were participating in our protocols nor have we found any adverse effects in frequently administered tests of physiological function while subjects were on protocol.

You will find a summary of our clinical data and results on page two of this letter. Our group has not presented this data in any formal presentations or papers. This data continues to be confidential. If you have any questions regarding this report, please contact Joseph K. Belanoff, M.D., at (650) 725-5586.

Sincerely,

Alan F. Schatzberg, M.D.
Kenneth T. Norris, Jr., Professor and Chairman
Department of Psychiatry and Behavioral Sciences
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AFS/brs

**EXHIBIT 1**

## Clinical Data and Results

**STUDY TITLE: "Rapid reversal of psychotic depression using mifepristone"**

**Number of subjects successfully completing protocol = 5**

This laboratory has observed in a current study that psychosis, altered cognition, and mood have all rapidly improved in patients with psychotic major depression when the glucocorticoid-receptor antagonist mifepristone was used for short periods. Our experimental protocol (in progress) calls for a four-day double-blind, placebo-controlled crossover study that uses 600 mg of mifepristone as the active agent. We have noted that because there is no intervening "washout period," there is a significant biochemical carryover effect.

In each of our first five cases, 21-item Hamilton Rating Scale for Depression[1] (HAM-D) scores declined during the 4 days of mifepristone treatment, on average 25.5% (i.e., from an average score of 31.4 → 23.4 on the last day). HAM-D scores remained essentially unchanged when the subjects received placebo during the first arm (before crossover) of the study (29.0 → 27.3). In both cases where subjects received mifepristone first, their HAM-D scores continued to decline in the placebo arm, in one case slightly and in the other case significantly.

On average, Brief Psychiatric Rating Scale[2] (BPRS) scores declined by 10.2 points (a change of 34.0%) while subjects were taking mifepristone. In contrast, average BPRS scores for the subjects administered placebo first increased by 3 points (5%). In one case where the subject received mifepristone first, the BPRS score continued a significant decline during the placebo period; in the other case, the subject's BPRS score rose to the pre-treatment level by the end of the placebo period.

Average Clinical Global Impression (CGI) scores declined by 33.0% (a decrease of 1.2 points on a seven-point scale, i.e., "much improved" relative to baseline) while subjects were taking mifepristone. For those subjects receiving placebo first, CGI scores declined by 8.0% (or 0.3 points). (Please refer to following summary on page 3.)

**STUDY TITLE: "Treatment of schizoaffective disorder using mifepristone"**

**Number of subjects successfully completing protocol = 2**

This double-blind, placebo-controlled clinical trial calls for research subjects with a diagnosis of schizoaffective disorder to be assigned randomly to receive *either* 400 mg mifepristone or placebo for eight days. Both subjects studied to date were randomized to the placebo arm of this study. In addition, both subjects chose to receive active medication (on an open-label basis for eight days) when the blind was broken at the conclusion of the randomized study protocol.

HAM-D, BPRS, and CGI scores did not change significantly in either patient when they were taking placebo or open-label mifepristone. Please see following summary of patient data.

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[1] Hamilton M: A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960; 23:56-62.
[2] Overall J, Gorham D: Brief Psychiatric Rating Scale. *Psychol Rep* 1962; 10:799.

## Raw Data

### RAPID REVERSAL OF PSYCHOTIC DEPRESSION USING MIFEPRISTONE (RU 486)

| Subject No. | Scale | Day 1 (raw score) | Day 5 (raw score) | Day 9 (raw score) | Δ |
|---|---|---|---|---|---|
| 1 | HAM-D | 29 | 21 | 10 | -19 |
| (RU486 first, | BPRS | 49 | 40 | 25 | -24 |
| then placebo) | CGI | 6 (severely depressed) | 6 | 3 (mildly depressed) | -3 |
| 2 | HAM-D | 33 | 35 | 21 | -12 |
| (placebo first, | BPRS | 51 | 57 | 44 | -7 |
| then RU486) | CGI | 6 (severely depressed) | 6 | 5 (markedly depressed) | -1 |
| 3 | HAM-D | 23 | 19 | 17 | -6 |
| (placebo first, | BPRS | 32 | 35 | 36 | +4 |
| then RU486) | CGI | 4 (moderately depressed) | 4 | 3 (mildly depressed) | -1 |
| 4 | HAM-D | 31 | 28 | 21 | -10 |
| (placebo first, | BPRS | 53 | 45 | 28 | -25 |
| then RU486) | CGI | 7 (extremely depressed) | 6 (severely depressed) | 5 (markedly depressed) | -2 |
| 5 | HAM-D | 46 | 37 | 35 | -11 |
| (RU486 first, | BPRS | 54 | 41 | 54 | 0 |
| then placebo) | CGI | 5 (markedly depressed) | 6 (severely depressed) | 4 (moderately depressed) | -1 |
| 6 | HAM-D | 41 | 35 | -- | -6 |
| (unknown, | BPRS | 49 | 42 | -- | -7 |
| in progress) | CGI | 6 (severely depressed) | 6 | -- | 0 |

### TREATMENT OF SCHIZOAFFECTIVE DISORDER USING MIFEPRISTONE

| Subject No. | Scale | Day 1 (raw score) | Day 9 (raw score) | Δ |
|---|---|---|---|---|
| 1 | HAM-D | 24 | 17 | -7 |
| (placebo) | BPRS | 47 | 53 | +6 |
| | CGI | 4 (moderately depressed) | 5 (markedly depressed) | +1 |
| 2 | HAM-D | 33 | 30 | -3 |
| (placebo) | BPRS | 51 | 46 | -5 |
| | CGI | 4 (moderately depressed) | 4 | 0 |

### OPEN-LABEL STUDY OF THE TREATMENT OF SCHIZOAFFECTIVE DISORDER USING MIFEPRISTONE

| Subject No. | Scale | Day 1 (raw score) | Day 9 (raw score) | Δ |
|---|---|---|---|---|
| 1 | HAM-D | 15 | 15 | 0 |
| | BPRS | 40 | 39 | -1 |
| | CGI | 3 (mildly depressed) | 4 (moderately depressed) | +1 |
| 2 | HAM-D | 28 | 21 | -7 |
| | BPRS | 50 | 49 | -1 |
| | CGI | 4 (moderately depressed) | 4 | 0 |